REMARKS

Introduction

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83-97 are pending in the above-referenced application. Applicant respectfully notes that Claims 76 and 77 should have been canceled by the amendment that was received and entered on November 30, 2005.

The Final Office Action mailed on February 22, 2006 notified applicant that the foreign priority patent application has yet to be filed. Claims 32, 37-39, 42-44, 49-51, 54, 56, 61-63, 67-70, 73-75, 78-80, and 83 are objected to as having incorrect status identifiers. Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 70, 75 and 80 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 73, 78 and 83 are rejected under 35 U.S.C. § 112, first paragraph. Claims 32, 34, 37-39, 44, 46, 49-51, 56, 58, 61-63, 66, 69, 70, 74, 75, 79 and 80 are rejected under 35 U.S.C. 103(a).

In response, Claims 32, 34, 37-39, 42-44, 49, 53, 56, 61, 65, 69, 73, 74, 79 and 83 have been amended. Claims 70, 75, 80, 91 and 92 have been canceled. Applicant has also amended the specification, page 12, to correct a spelling error. In view of the foregoing, applicant respectfully requests reconsideration and allowance of all claims pending in the application.

Priority

The Office Action acknowledges a foreign priority claim based on an application filed in Japan on September 9, 1999 (11-255024). The Office Action notes that a certified copy of the Japan patent application, as required by 35 U.S.C. § 119(b), has not been filed. Applicant submitted the priority document during the International Phase as evidenced by the attached copy of Form PCT/IB/304. For this reason, applicant believes that no further action is required.

Claim Objections

Claims 32, 37-39, 42-44, 49-51, 54, 56, 61-63, 67-70, 73-75, 78-80, and 83 are objected to as having incorrect status identifiers. The claims were identified as "Withdrawn" or

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"Withdrawn-currently amended." The Office Action requires Applicant to use the proper status identifiers pursuant to 37 C.F.R. § 1.121. These claims have been amended to use the proper status identifiers.

Claim Rejections Under 35 U.S.C. § 112

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83 are rejected as indefinite because it is unclear what is meant by "perforation of the membrane recovers to the state prior to perforation." In response, Claims 32, 44, and 56 have been amended to recite "the membrane recovers to its state prior to perforation." Support for this amendment is found in the specification, page 2, lines 3-5; page 5, lines 1-2; see also page 13, first full paragraph.

Claims 53 and 65 are rejected as indefinite. Claims 53 and 65 are currently amended in accordance with the Examiner's suggestion. Applicant appreciates Examiner's assistance with this correction.

Claims 73 and 83 are rejected as indefinite because they recite "the capillary" without antecedent basis. Claims 73 and 83 have been amended. A proper antecedent basis is now established in the claims as currently amended.

New Matter Under 35 U.S.C. § 112, First Paragraph

Claims 70, 75, and 80 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action states that Claims 70, 75 and 80 have been amended to require permeabilization of a membrane by the method of Claim 32, 44 or 56, i.e., by bringing a photosensitizer or photocatalyst into close contact or proximity with the membrane and providing stimulatory light for the photosensitizer or photocatalyst. The Office Action also states that Claims 70, 75 and 80 further recite "injecting a desired substance inside the membrane" (page 5).

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The Office Action states that there are two ways to interpret these claims. In the first interpretation, Claims 70, 75 and 80 fail to further limit Claims 32, 44 or 56. In the second interpretation, Claims 70, 75 and 80 introduce new matter into the disclosure (page 6).

Applicant notes that Claims 70, 75 and 80 do not in fact recite "injecting a desired substance inside the membrane," as stated in the Office Action. Instead, Claims 69, 74 and 79 recite "injecting a desired substance inside the membrane."

Nonetheless, in response to Examiner's comments, Claims 70, 75 and 80 have been canceled. Claims 69, 74 and 79 have been amended to further limit Claims 32, 44 and 56, respectively. Claims 69, 74 and 79 now recite "injecting a desired substance inside the membrane, wherein said substance to be injected inside said membrane comprises a photosensitizer or photocatalyst as a membrane denaturing substance that induces a membrane-denaturing reaction by light as a stimulus, and an additional substance." The amendments to Claims 69, 74 and 79 further limit Claims 32, 44 and 56. The amendments do not introduce new matter into the claims; support for the amendments may be found on page 9 of the specification, last full paragraph.

Scope of Enablement Under 35 U.S.C. § 112, First Paragraph

Claims 73, 78, and 83 are rejected under 35 U.S.C. § 112, first paragraph. The Office Action states that the specification, while being enabling for methods as claimed wherein a capillary is caused to penetrate a cell membrane or artificial membrane, does not reasonably provide enablement for such methods in which a capillary is made to penetrate an intracellular membrane. The Office Action states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims (page 6).

The Office Action states that although Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements (page 7). The composition of cell membranes, including

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intracellular membranes, is well known to be a phospholipid bilayer. According to Wikipedia, an online encyclopedia, "a cell membrane (or plasma membrane or plasmalemma) is the part of any biological cell that covers the cell. It is selectively permeable, structured bilayer of phospholipid and protein molecules" (http://en.wikipedia.org/wiki/Cell_membrane). As for intracellular membranes, "the endomembrane system is the system of internal membranes within eukaryotic cells that divide the cell into functional and structural compartments, or organelles. The membranes that make up the endomembrane system are made of a lipid bilayer, with proteins attached to either side or traversing them" (http://en.wikipedia.org/wiki/Endomembrane_system).

According to Molecular Biology of the Cell (4th ed., 2002, page 584), "[t]he lipid bilayer has been firmly established as the universal basis for cell-membrane structure." Organelle membranes also have a lipid bilayer (Molecular Biology of the Cell, 4th ed., 2002, page 660). Therefore, because both a cell membrane and an intracellular membrane (or internal membrane) are comprised of a phospholipid bilayer, perforation of an intracellular membrane can be done using the method of Claims 73, 78 or 83, and the critical elements of the invention as well as how to use those elements are disclosed in the specification.

The Office Action states that the prior art of record offers no example of penetrating an intracellular membrane with a capillary as required by the instant claims (page 7). In response, Applicant is currently submitting a new reference to be included in the Information Disclosure Statement. The new reference (M. Knoblauch et al., "A Galinstan Expansion Femtosyringe for Microinjection of Eukaryotic Organelles and Prokaryotes," *Nature Biotechnology 17*:906-909, September 1999), a copy of which is enclosed, describes injection of a substance inside a cell nuclear membrane using a capillary.

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Claim Rejections Under 35 U.S.C. § 103

Claims 32, 34, 37-39, 44, 46, 49-51, 56, 58, 61-63, 66, 69, 70, 74, 75, 79, and 80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Berg et al. (WO 96/07432), in view of Chen et al. (U.S. Patent 5,445,608). Applicant respectfully disagrees.

Three basic criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In addition, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.02. (emphasis in original). *See also W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

For the reasons set forth below, applicant respectfully submits that the burden of establishing a *prima facie* case of obviousness has not been met because the combined prior art references do not teach or suggest all of the claim limitations, and because there is no suggestion or motivation to combine the references' teachings.

Berg discloses a method of transporting molecules into the cytosol of living cells by exposing the cells to a photoactivatable compound which is taken up by the cell and located in endosomes or lysosomes. Berg's method relies on cellular endocytosis to bring the photosensitizer and the molecules of choice into the same vesicle. Next, the cells are exposed to light of a suitable wavelength to activate the photosensitizing compound such that the endosomal, lysosomal or other intracellular compartment membranes are ruptured and the molecules are released into the cytosol (WO 96/07432, pages 5-6; Fig. 1 description, page 3).

The Office Action admits that Berg does not teach a membrane-destroying member as in Claim 32, a supporting member that brings a photosensitizer or photocatalyst and carries light

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from a light source as in Claim 44, or a stimulus carrying member that locally introduces light to a site in the membrane as in Claim 56 (Office Action, page 9, first full paragraph).

In addition, Berg fails to disclose a method of perforating a cell membrane, as in Claims 32, 44 and 56. As stated above, Berg's method relies on cellular endocytosis to bring the photosensitizer and the molecules inside a vesicle. The cellular process of endocytosis brings the molecules inside the vesicle, and therefore inside the cell, before they are released into the cytosol. This differs from a method of perforating a membrane which is done without relying on cellular endocytosis, as in Claims 32, 44 and 56.

Berg also fails to disclose that the membrane recovers to the state prior to perforation, as in Claims 32, 44 and 56. Although Berg discloses that the endosomal or lysosomal membranes are ruptured, the only criteria for the cell is that it does not lose its functionality (Berg, page 2, last paragraph). A cell could survive the rupture of an endosome or lysosome without losing its functionality. Therefore, Berg need not contemplate whether the membrane damage is reversible because the damage is done to an intracellular membrane, not the outer cell membrane, which does not necessarily result in a loss of cellular function.

The deficiencies of the Berg reference are not cured by the teachings of the Chen reference. Chen discloses a method and apparatus for photodynamic therapy of tissue by supplying light to a treatment site that has selectively absorbed a photoreactive agent perfused into it (Column 1, lines 6-11). Chen discloses a catheter that is disposed within a patient's body to supply photoreactive agent to the site of treatment (Column 4, lines 7-16). Chen also discloses an optical fiber as a light source than can be placed within the catheter in the annular flow channel (Column 23, lines 43-53).

The Office Action states that in Chen the catheter functions as a capillary and the optical fiber functions as a membrane-destroying member, a supporting member and a stimulus carrying member. Although Chen discloses a method and apparatus using light and a photoreactive agent, Chen is concerned with tissue-level therapy, not a method of perforating a membrane, as in

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Claims 32, 44 and 56. Chen's method and apparatus do not relate to membrane perforation, but to the destruction of cancerous cells (Column 1, lines 11-12).

Moreover, Chen does not disclose bringing a membrane-denaturing substance into contact with or close proximity with a membrane, as in Claims 32, 44 and 56. Instead, Chen discloses "infusing the photoreactive agent into the treatment site" (Column 5, lines 9-11) where "[a] tumor comprising abnormal cells is known to selectively absorb certain dyes perfused into the site to a much greater extent than surrounding tissue" (Column 1, lines 15-17). Therefore, although Chen discloses the use of a catheter and optical fiber, these are not similar to a capillary, a membrane-destroying member, a supporting member and a stimulus carrying member because the scale of use (i.e., tissue-level versus cell-level) is entirely different. Chen may be able to precisely illuminate a tumor at the site of photosensitizer delivery, but this is not the same as providing light stimulus to a substance for perforating a membrane, as in Claims 32, 44 and 56.

Furthermore, Chen does not disclose or suggest that the membrane recovers to the state prior to perforation, as in Claims 32, 44 and 56. Chen instead is concerned with the destruction of tumor cells and has no reason to provide for membrane recovery.

Berg and Chen collectively therefore fail to teach or suggest all of the claim limitations. For example, neither Berg nor Chen discloses a method of perforating a membrane comprising bringing a membrane-denaturing substance into contact with or close proximity to at least a site of the membrane. As another example, neither Berg nor Chen discloses perforating a membrane where the member recovers to the state prior to perforation, as in Claims 32, 44 and 56.

The Office Action further states that it would have been obvious to use the apparatus of Chen in the method of Berg because the apparatus of Chen allows precise illumination at the site of photosensitizer delivery. However, Berg is concerned with cells, while Chen is concerned with tissue. There would be no motivation to combine the apparatus of Chen, which is meant to

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be used with tissue, in the method of Berg, which is used for cells, because both the scale of the apparatus and the methods used are entirely different.

In view of the above argument, applicant submits that the subject claims are not rendered obvious over Berg, either alone or in combination with Chen. Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully submits that all pending claims are in condition for allowance. If the Examiner has any questions, the Examiner is invited to contact Applicant's attorney at the number provided below.

Respectfully submitted,

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